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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/801,371	03/07/2001	Raymond Kaempfer	A34084 PCT USA-A	9946

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EXAMINER
WHITEMAN, BRIAN A

ART UNIT	PAPER NUMBER
1635	16

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/801,371	Applicant(s) KAEMPFER ET AL.	
	Examiner Brian Whiteman	Art Unit 1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *1* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____ .

2a)☐ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-50* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) _____ is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *1-50* are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Claims 1-50 are pending.

Election/Restrictions

Restriction to one of the following inventions is required under 35 U.S.C. 121 and an election to one of the following species beginning on page 9 is required under 35 U.S.C. 121:

I. Claims 1-31 and 47-49, drawn to a cis-acting nucleotide sequence, which is capable of removing the intron(s) from a pre-cursor transcript encoded by a gene; a DNA construct comprising a cis-acting nucleotide sequence and a gene, which encodes a protein selected from the group consisting of enzymes, hormones, growth factors, cytokines, structural proteins, or industrially or agriculturally applicable proteins, and also encodes one intron; a vector comprising a cis-acting nucleotide sequence and a gene which encodes one intron or a DNA construct comprising a cis-acting nucleotide sequence and a gene which encodes one intron, a host cell transfected with said vector described above, a pharmaceutical composition comprising said expression vector or transformed host cells described above, classifiable in class 536, subclass 23.1 and class 435, subclass 320.1.

II. Claims 32-33 and 50, drawn to a method of producing a recombinant enzyme, hormone, cytokine, structural protein, or industrially or agriculturally applicable protein comprising the steps of providing a transgenic animal, wherein its genome comprises a DNA construct according to any one of claim 7 to 22, wherein DNA construct comprises of a cis-acting nucleotide sequence and a gene encoding a

recombinant enzyme, hormone, cytokine, structural protein, or industrially or agriculturally applicable protein, classifiable in class 800, subclass 4 and subclass 8.

Note: If applicants elect Group II, a further restriction follows in sub-groups I-VII:

I. enzymes,

a.) Furthermore, applicants are required to elect a specific enzyme.

II. hormones,

a.) Furthermore, applicants are required to elect a specific hormone.

III. growth factors,

a.) Furthermore, applicants are required to elect a specific growth factor.

IV. cytokines,

a.) Furthermore, applicants are required to elect a specific cytokine.

V. structural proteins,

a.) Furthermore, applicants are required to elect a specific structural protein.

VI. industrially,

a.) Furthermore, applicants are required to elect a specific industrially applicable protein.

VII. agriculturally applicable proteins,

a.) Furthermore, applicants are required to elect a specific agriculturally applicable protein.

III. Claims 34-35, 37-38, and 43-45, drawn to a method of regulating gene expression at the mRNA splicing level comprising the steps of: a) providing a cis-acting nucleotide sequence, which is capable of removing intron(s) from a pre-cursor transcript encoded by a gene, which contains at least one intron dependent upon activation of a trans-acting factor, said trans-acting factor being an RNA activated protein kinase which is capable of phosphorylating the alpha subunit of eukaryotic initiation factor 2, wherein the activation of the RNA-activated eIF2alphakinase in the host cell is chemically modulated, b) operably linking said cis-acting sequence to said gene, c) optionally linking to nucleotide sequence from step b) additional expression controls, d) transfecting a host cell with the nucleotide sequence from step b) or step c); a method of providing a therapeutic protein to a mammal comprising administering to the mammal a DNA construct comprising a cis-acting nucleotide sequence and a gene, which encodes one intron and encodes a therapeutic protein, classifiable in class 435, subclass 320.1 and class 514, subclass 44.

IV. Claims 34, 36, and 43-45, drawn to a method of regulating gene expression at the mRNA splicing level comprising the steps of: a) providing a cis-acting nucleotide sequence, which is capable of removing intron(s) from a pre-cursor transcript encoded by a gene, which contains at least one intron dependent upon activation of a trans-acting factor, said trans-acting factor being an RNA activated protein kinase which is capable of phosphorylating the alpha subunit of eukaryotic initiation factor 2, wherein the activation of the RNA-activated eIF2alphakinase

in the host cell is modulated by use of a trans-dominant negative mutant of PKRalpha6, b) operably linking said cis-acting sequence to said gene, c) optionally linking to nucleotide sequence from step b) additional expression controls, d) transfecting a host cell with the nucleotide sequence from step b) or step c); a method of providing a therapeutic protein to a mammal comprising administering to the mammal a DNA construct comprising a cis-acting nucleotide sequence and a gene, which encodes one intron and encodes a therapeutic protein, classifiable in class 435, subclass 320.1 and class 514, subclass 44.

V. Claims 34 and 39-45, drawn to a method of regulating gene expression at the mRNA splicing level comprising the steps of: a) providing a cis-acting nucleotide sequence, which is capable of removing intron(s) from a pre-cursor transcript encoded by a gene, which contains at least one intron dependent upon activation of a trans-acting factor, said trans-acting factor being an RNA activated protein kinase which is capable of phosphorylating the alpha subunit of eukaryotic initiation factor 2, wherein the activation of the RNA-activated eIF2alphakinase in the host cell is modulated by use of a vector expressing viral proteins, b) operably linking said cis-acting sequence to said gene, c) optionally linking to nucleotide sequence from step b) additional expression controls, d) transfecting a host cell with the nucleotide sequence from step b) or step c); a method of providing a therapeutic protein to a mammal comprising administering to the mammal a DNA construct comprising a cis-acting nucleotide sequence and a

gene, which encodes one intron and encodes a therapeutic protein, classifiable in class 435, subclass 320.1 and class 514, subclass 44.

VI. Claims 43-44 and 46, drawn to an ex vivo method of providing a therapeutic protein to a mammal comprising administering to the mammal a genetically modified cell comprising a DNA construct comprising a cis-acting nucleotide sequence and a gene, which encodes one intron, classifiable in class 424, subclass 93.

Claim 34 links invention III-V. The restriction requirement between the linked inventions is subject to the non-allowance of the linking claim(s), claim 34. Upon the allowance of the linking claim(s), the restriction requirement as to the linked inventions shall be withdrawn and any claim(s) depending from or otherwise including all the limitations of the allowable linking claim(s) will be entitled to examination in the instant application. Applicant(s) are advised that if any such claim(s) depending from or including all the limitations of the allowable linking claim(s) is/are presented in a continuation or divisional application, the claims of the continuation or divisional application may be subject to provisional statutory and/or non-statutory double patenting rejections over the claims of the instant application. Where a restriction requirement is withdrawn, the provisions of 35 U.S.C. 121 are no longer applicable. *In re Ziegler*, 44 F.2d 1211, 1215, 170 USPQ 129, 131-32 (CCPA 1971). See also MPEP § 804.01.

The inventions are distinct for the following reasons:

As set forth in *In re Harnisch* (631F.2d 716 206 USPQ 300 (CCPA 1980), see MPEP 803.02, unity of invention exists for all species in a claim (1) shows a common utility, and (2) share a substantial structural feature disclosed as being essential to that utility.

In view of *In re Harnisch*, claims 34-42 lack unity of invention for the following reasons: 1) the activation of the RNA-activated eIF2 alpha kinase in said host cell is modulated by use of a chemically modulated (e.g. set forth in claim 35, 37, or 38), a trans-dominant negative mutant (set forth in claim 36), and a vector expressing either viral proteins or viral RNA (set forth in claims 39-42). Each modulated does not share a substantial structural feature disclosed as being essential for that utility. Therefore in view of In re Harnisch, claims 34-42 lack unity of invention and are separated into distinct groups as shown in the groups set forth above.

In addition, as set forth in *In re Harnisch* (631F.2d 716 206 USPQ 300 (CCPA 1980), see MPEP 803.02, unity of invention exists for all species in a claim (1) shows a common utility, and (2) share a substantial structural feature disclosed as being essential to that utility.

In view of *In re Harnisch*, claims 32-33 and 50 lack unity of invention for the following reasons: 1) a transgenic animal carrying a DNA construct according to any of claims 7 to 22. Each species of genes (e.g. enzymes, hormones, growth factors, cytokines, structural proteins, industrially, or agriculturally applicable proteins) do not share a common utility and do not share a substantial structural feature disclosed as being essential for that utility. More specifically, each specific gene used in making a non-human transgenic would display a distinct phenotype when expressed in the transgenic animal, therefore each gene would not share a substantial structural feature disclosed as being essential for each transgenic animal comprising the specific

gene. Therefore in view of In re Harnisch, claims 32-33 and 50 lack unity of invention and are further separated into distinct groups as shown in subgroups I-VII.

Although there are no provisions under the section for "Relationship of Inventions" in MPEP 806.05 for inventive groups that are directed to different methods, restriction is deemed to be proper because each of the methods of inventions II and III-VI, constitutes patentably distinct inventions for the following reasons: Each of the inventions is directed to different goals and comprises materially distinct steps, wherein each of the compositions in each invention is structurally distinct and/or generates distinct mechanisms and functional effects as indicated above. The scope of each of the cited inventions encompasses an employed method, which generates distinct function(s) and effect(s), and furthermore does not necessarily overlap with that of another invention. For example, Invention VI is an *ex vivo* method of gene therapy and Inventions III-V are directed to distinct *in vivo* methods of gene therapy, which comprise of using distinct modulators and each invention employs a distinct method, which generates a distinct function and effect. Thus, inventions II and III-VI comprise materially distinct steps, and/or generate different functions and effects, and thus, are not required for use with one another. Therefore, the invention of groups II and III-VI are distinct.

Inventions I and II-VI are related as product and process of use. The inventions can be shown to be distinct if either or both of the following can be shown: (1) the process for using the product as claimed can be practiced with another materially different product or (2) the product as claimed can be used in a materially different process of using that product (MPEP § 806.05(h)). In the instant case, invention I is drawn to a cis-acting nucleotide sequence, which is capable of removing the intron(s) from a pre-cursor transcript encoded by a gene; a DNA

construct comprising a cis-acting nucleotide sequence and a gene, which encodes a protein selected from the group consisting of enzymes, hormones, growth factors, cytokines, structural proteins, or industrially or agriculturally applicable proteins. The nucleotide sequence or the construct comprising the nucleotide sequence of inventions I can be used in distinct and materially different processes as exemplified in Groups II-VI.

This application contains claims directed to the following patentably distinct species of the claimed invention: a gene, which encodes a protein wherein the protein is selected from the group consisting of enzymes, hormones, growth factors, cytokines, structural proteins, industrially, or agriculturally applicable proteins set forth in claims 6, 11, and 50.

Applicant is required under 35 U.S.C. 121 to elect a single disclosed species for prosecution on the merits to which the claims shall be restricted if no generic claim is finally held to be allowable. Currently, claims 1, 7, 34, and 50 are generic.

Applicant is advised that a reply to this requirement must include an identification of the species that is elected consonant with this requirement, and a listing of all claims readable thereon, including any claims subsequently added. An argument that a claim is allowable or that all claims are generic is considered nonresponsive unless accompanied by an election.

Upon the allowance of a generic claim, applicant will be entitled to consideration of claims to additional species which are written in dependent form or otherwise include all the limitations of an allowed generic claim as provided by 37 CFR 1.141. If claims are added after the election, applicant must indicate which are readable upon the elected species. MPEP § 809.02(a).

Should applicant traverse on the ground that the species are not patentably distinct, applicant should submit evidence or identify such evidence now of record showing the species to be obvious variants or clearly admit on the record that this is the case. In either instance, if the examiner finds one of the inventions unpatentable over the prior art, the evidence or admission may be used in a rejection under 35 U.S.C. 103(a) of the other invention.

Because these inventions are distinct for the reasons given above and the literature search required for Group I is not required for Groups II-VI, restriction for examination purposes as indicated is proper.

It would be unduly burdensome for the examiner to search and consider patentability of all of the presently pending claims, a restriction for examination purposes as indicated is proper.

Applicant is advised that the reply to this requirement to be complete must include an election of the invention to be examined even though the requirement be traversed (37 CFR 1.143).

Applicant is reminded that upon cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 C.F.R. § 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a diligently filed petition under 37 C.F.R. § 1.48(b) and by the fee required under 37 § 1.17(h).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Kay Pinkney whose telephone number is (703) 305-3553.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Brian Whiteman whose telephone number is (703) 305-0775.

The examiner can normally be reached on Monday through Friday from 8:00 to 5:00 (Eastern Standard Time), with alternating Fridays off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's mentor, primary examiner, Dave Nguyen can be reached at (703) 305-2024.

If attempts to reach the primary examiner by telephone are unsuccessful, the examiner's supervisor, John L. LeGuyader, SPE - Art Unit 1635, can be reached at (703) 308-0447.

Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center number is (703) 308-2742.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-8724.

Brian Whiteman
1635
4/5/02

DAVE T. NGUYEN
PRIMARY EXAMINER